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NEW 1-SUBSTD.-4-PHENYL-3-(2-OXO-ALKYLIDENE)-2-AZETIDINONE DERIVS. + USEFUL AS BLOOD PLATELET AGGREGATION INHIBITORS, PREPD. FROM 4-PHENYL-2,3-AZETIDINE-DI:ONE(S) AND WITTIG REAGENT

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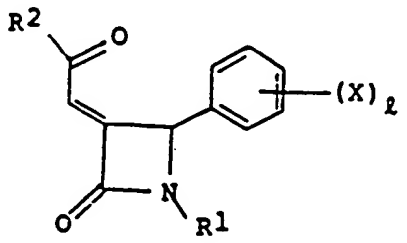
(54) Azetidinone derivatives.

(AW) OXO ALKYLIDENE

(57) 2-Azetidinone derivatives represented by the following formula



wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, ℓ is 1 or 2, R^1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, an

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optionally substituted phenethyl group, an optionally substituted phenyl group, an optionally substituted benzyl group or a bis(alkoxycarbonyl)ethyl group, and R^2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxycarbonylmethyl group or an optionally substituted phenyl group, are useful as blood platelet aggregation inhibiting agents.

AZETIDINONE DERIVATIVES

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The present invention relates to 2-azetidinone derivatives having blood platelet aggregation inhibiting activity.

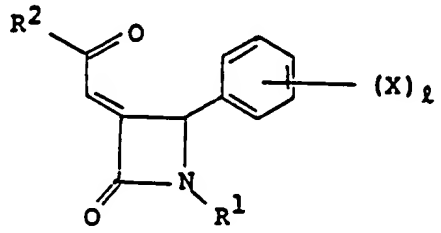
2. DESCRIPTION OF THE PRIOR ART

Although some compounds having azetidinone skeleton which show antibacterial activity have been known in the past, any azetidinone derivative showing blood platelet aggregation inhibiting activity has not been yet reported.

SUMMARY OF THE INVENTION

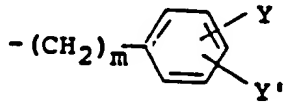
As a result of earnest researches to blood platelet aggregation inhibiting activity of the compounds having an azetidinone skeleton, the present inventors have found novel 2-azetidinone derivatives having blood platelet aggregation inhibiting activity, and the present invention has been completed.

An object of the present invention is to provide 2-azetidinone derivatives represented by the general formula

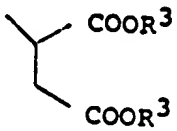


I

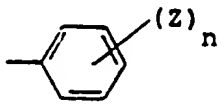
wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, ℓ is 1 or 2, R^1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula



(wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula



(wherein R^3 is a lower alkyl group), and R^2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxycarbonylmethyl group, a group of the formula



(wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

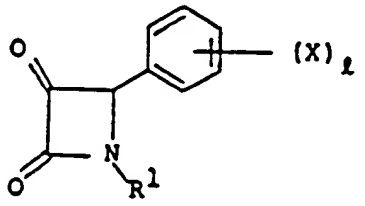
Other object of the present invention is to provide blood platelet aggregation inhibiting agents containing the compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the term "lower alkyl group" refers to straight or branched chain alkyl group having 1 to 4 carbon atoms such as, for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a tert-butyl group and the like. The term "cycloalkyl group" refers to a cyclopentyl group and a cyclohexyl group. The term "lower alkoxy group" refers to those having 1 to 3 carbon atoms such as, for example, a methoxy group, an ethoxy group, a propoxy group and the like. The term "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. The term "lower alkoxycarbonylmethyl group" refers to those such as, for example, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group and the like.

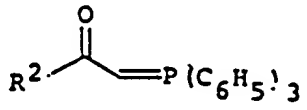
Preferred compounds of formula I are those wherein X is a hydrogen atom, R^1 is a benzyl group or a chlorobenzyl group, and R^2 is a nitrophenyl group.

The compounds of the present invention can be easily prepared, for example, by a reaction (i.e., Wittig Reaction) of a compound represented by the general formula



II

wherein R^1, X and l are as defined above, with a Wittig reagent represented by the general formula



III

wherein R^2 is as defined above.

Reaction solvents used in this reaction are those used in the ordinary Wittig Reaction such as, for example, benzene, ethyl ether, tetrahydrofuran, toluene, chloroform, methylene chloride, dimethoxyethane and the like. The reaction temperature is from -30°C to the temperature of the boiling point of the solvent used, preferably from 0°C to 30°C. The reaction time depends on the starting material, the Wittig reagent or the reaction temperature, but usually it is from 2 to 48 hours, and the reaction may be stopped after the disappearance of the starting material observed by using thin layer silica gel column chromatography.

Configuration of the oxyalkylidene substituent of especially useful compounds of the present invention is E-form, and the configuration due to the asymmetric carbon atom at the 4-configuration is dl-form.

Some of the compounds of formula II are known, and some are new and can be prepared by the methods described in the literature [e.g., Tetrahedron Letters, Vol. 25 (No. 42), page 4733 (1984)].

It is recognized that the compounds of the present invention have excellent blood platelet aggregation inhibiting activity and very poor bleeding tendency as side-effect, and therefore, they are useful as blood platelet aggregation inhibiting agents. For the purpose, these compounds can be administered orally or parenterally in a conventional dosage form such as tablets, powders, granules, capsules, solutions, emulsions, suspensions, injectional solutions and the like, each of which can be prepared by conventional pharmaceutical practices.

The dosage used as blood platelet aggregation inhibiting agents to human depends on the age, weight or response of patient, administration route or time of administration, but usually it may be from 10 to 3000 mg per day.

The LD_{50} of the compound of formula I in mouse is more than 5000 mg/kg.

Next, the following experiments illustrate concretely excellent blood platelet aggregation inhibiting activity and prolongation effect of bleeding time of the compound of the present invention.

Experiment 1 [invitro test in rabbit]

Citrated blood (one volume of 3.2% sodium citrate: 9 volumes of blood) was collected from carotid artery of male, New Zealand strain house rabbit, centrifuged at 150 g for 15 minutes to give platelet rich plasma (PRP) as a supernatant, and the remaining blood was centrifuged at 1500 g for 10 minutes to give platelet poor plasma (PPP) as a supernatant. The platelet count of PRP was adjusted to 50 - 60 * 10^4/µl by dilution of PPP. Blood platelet aggregation was carried out according to the method of Born [Born, G.V.R., Nature, 194, 927 (1962)]. Namely, 25 µl of the test drug, (all the test drugs were dissolved in dimethyl sulfoxide and adjusted to the desired concentration with physiological saline solution), was added to 250 µl of PRP, and the mixture was incubated at 37°C for 3 minutes. 25 µl of the aggregation inducing substance [adenosine diphosphate (ADP): final concentration 5 µM or collagen: final concentration 5 µg/ml] was added, the mixture was measured for 5 minutes by blood platelet aggregation ability measurement apparatus (Aggricoda TM-PA-3210, Kyoto Dai-ichi Kagaku) to obtain the maximum aggregation rate, and there was calculated the concentration of the test drug (IC_{50}) which brings about 50% inhibition to the maximum aggregation rate obtained by adding the aggregation inducing substance to PRP containing the solvent only.

The compound numbers in Table 1 correspond to those in the Examples described below.

Table 1

Compound No.	IC_{50} (x µM)		Compound No.	IC_{50} (x µM)	
	ADP	Collagen		ADP	Collagen
1	33	14	43	14.0	7.7
2	28	32	44	10.3	7.3
4	13	16	45	4.4	5.2
5	24	23.5	52	7.9	-
6	24	18	53	4.9	-
7	12	23	54	11.2	15.5
8	9.2	13.6	55	10.5	8.3
9	15	12	56	2.9	6.5
10	36	26	67	27.7	11.0
11	>30	22	68	13.6	7.5
12	5.6	4.7	75	3.8	5.4
15	21.5	16.6	76	14.3	10.5
16	12.5	4.1	77	4.3	2.9
17	7.7	5.0	78	6.2	8.3
18	6.6	3.2	79	4.3	5.1
21	30.9	-	80	7.4	10.9
22	41.3	-	81	5.5	7.0
24	6.4	-	85	17.7	14.4
25	11.1	6.6	86	6.2	5.3
26	16.5	9.5	91	9.7	6.7
29	9.0	8.1	92	7.3	6.5
32	3.5	3.8	93	18.3	8.7
33	11.9	12.5	94	8.0	6.9
34	8.2	6.6	95	15.4	2.5
37	21.2	17.8	96	3.9	3.7
38	9.0	4.6	97	16.0	3.2
39	>30	>30	98	11.2	8.8
40	11.3	13.2	103	18.5	6.7
41	4.2	5.1	papaverin	>100	>100

Experiment 2 [prolonging test of the bleeding time in mouse]

Six male ICR strain mice weighing 20 g for each group were administered orally with 300 mg/kg of the test drug (all the test drugs were used in the form of the suspension in 0.5% CMC). Two hours after administration, 5 mm of the tail from the top was cut under pentobarbital anesthesia, and the bleeding was observed by tapping at the cutting site with a filter paper every 15 seconds. The time when the bleeding was observed stopping for one minute is defined as the arrest point of bleeding, and the duration required from the time when the cutting was done to the arrest point of bleeding is defined as the bleeding time. The observation was carried out up to 1200 seconds. Ticlopidine was used as a positive control.

The results were shown in Table 2. The compound numbers in Table 2 correspond to those in the Examples described below.

Table 2

Compound No.	Bleeding time ± standard error
53	270.0 ± 54.08
56	277.5 ± 36.90
ticlopidine	1127.5 ± 72.50 (note)
the solvent	305.0 ± 77.23

(Note) $P < 0.05$ by Mann and Whitney's U test.

The following Examples illustrate the method for preparing the compound of the present invention in more detail.

Example 1

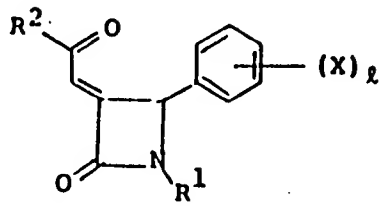
Preparation of (E)-3-(2-oxopropylidene)-1,4-diphenyl-2-azetidinone (Compound 1)

To a solution of 0.67 g of acetylmethylene triphenylphosphorane in 70 ml of benzene was added at room temperature under a nitrogen atmosphere a solution of 0.50 g of 1,4-diphenyl-2,3-azetidinedione in 30 ml of benzene, and the mixture was stirred overnight. After completion of the reaction, the benzene was evaporated, and the residue was applied to silica gel column chromatography (eluent; methylene chloride). The desired fractions were combined, the solvent was evaporated, and the residue was recrystallized from ethanol to give the title compound as pale yellow needles. Yield 0.32 g, m.p. 157.5 - 158.5°C

Example 2

Following the similar procedure of that of Example 1, there were obtained the compounds 2 to 118, which were listed in Table 3 including the compound obtained in Example 1.

Table 3



Compound No.	$(X)_\ell$	R^1	R^2	m.p. (°C)
1	H	phenyl	methyl	157.5-158.5
2	H	phenyl	ethyl	149-150.5
3	H	phenyl	ethoxy	130.5-132.5
4	H	phenyl	phenyl	226-227
5	H	phenyl	p-methylphenyl	174-177
6	H	phenyl	p-methoxyphenyl	227.5-228.5
7	H	phenyl	o,p-dimethoxy-phenyl	147.5-150
8	H	phenyl	p-fluorophenyl	222-223
9	H	phenyl	p-chlorophenyl	239.5-241
10	H	phenyl	p-bromophenyl	250.5-256

- Cont'd -

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Table 3 (Cont'd)

11	H	phenyl	p-biphenyl	250-250.5
12	H	phenyl	p-nitrophenyl	235.5-236.5
13	H	phenyl	amino	212-213
14	H	phenyl	1-adamantyl	198.5-200
15	H	phenyl	ethoxycarbonyl-methyl	154.5-159.5
16	H	o-methylphenyl	p-methoxyphenyl	142-144
17	H	o-methylphenyl	p-fluorophenyl	140.4-141.9
18	H	o-methylphenyl	p-nitrophenyl	199.5-200.4
19	H	2,6-dimethylphenyl	p-fluorophenyl	188-189.5
20	H	2,6-dimethylphenyl	p-nitrophenyl	300 or above
21	H	o-methyl-p-chlorophenyl	p-methylphenyl	142-144
22	H	o-methyl-p-chlorophenyl	p-methoxyphenyl	147-148.5
23	H	o-methyl-p-chlorophenyl	p-fluorophenyl	172-174
24	H	o-methyl-p-chlorophenyl	p-nitrophenyl	195-196
25	H	2-methyl-5-chlorophenyl	methyl	149.5-151.5

- Cont'd -

Table 3 (Cont'd)

26	II	2-methyl-5-chlorophenyl	phenyl	145-147
27	II	2-methyl-5-chlorophenyl	p-fluorophenyl	140-142
28	II	2-methyl-5-chlorophenyl	p-nitrophenyl	195.5-197
29	II	p-fluorophenyl	phenyl	206-208.5
30	II	p-fluorophenyl	p-fluorophenyl	211-213
31	II	p-fluorophenyl	p-chlorophenyl	221.5-224
32	II	p-fluorophenyl	p-nitrophenyl	204.5-207
33	II	o-fluorophenyl	p-fluorophenyl	180.5-183
34	II	o-fluorophenyl	p-nitrophenyl	219.7-221
35	II	o-chlorophenyl	p-fluorophenyl	146-147.5
36	II	o-chlorophenyl	p-nitrophenyl	189-191
37	II	3,5-dichlorophenyl	p-fluorophenyl	200.2-201.5
38	II	3,5-dichlorophenyl	p-nitrophenyl	206 (decompos. ion)
39	II	p-bromophenyl	p-methoxyphenyl	208-209
40	II	p-bromophenyl	p-fluorophenyl	211.5-213

- Cont'd -

Table 3 (Cont'd)

41	H	p-bromophenyl	p-nitrophenyl	222-224
42	H	o-methoxyphenyl	p-nitrophenyl	219-221.2
43	H	m-trifluoromethylphenyl	phenyl	174-177
44	H	m-trifluoromethylphenyl	p-fluorophenyl	159.5-161
45	H	m-trifluoromethylphenyl	p-nitrophenyl	181.5-184
46	H	p-dimethylaminophenyl	p-nitrophenyl	168-170
47	H	p-carboxylphenyl	p-fluorophenyl	300 or above
48	H	p-dichloroacetylphenyl	p-fluorophenyl	180.5-183.5
49	H	p-dichloroacetylphenyl	p-nitrophenyl	190.5-192.5
50	H	benzyl	methyl	76.5-78.5
51	H	benzyl	phenyl	111.5-113.5
52	H	benzyl	p-fluorophenyl	105-107.5
53	H	benzyl	p-nitrophenyl	122-126
54	H	o-chlorobenzyl	methyl	78-79
55	H	o-chlorobenzyl	p-fluorophenyl	74-76

- Cont'd -

Table 3 (Cont'd)

56	H	o-chlorobenzyl	p-nitrophenyl	113-115
57	H	1(S)-phenethyl	p-nitrophenyl	127.5-130.5
58	H	1-carboxy-2-phenethyl	p-fluorophenyl	250-255
59	H	propyl	p-fluorophenyl	88.5-91
60	H	propyl	p-nitrophenyl	127.5-130.5
61	H	cyclohexyl	methyl	124-127
62	H	cyclohexyl	p-fluorophenyl	125-126.5
63	H	cyclohexyl	p-nitrophenyl	199-202.5
64	H	1,2-bis(methoxycarbonyl)-ethyl	p-fluorophenyl	126-128
65	p-methyl	phenyl	p-fluorophenyl	208.5-211
66	p-methyl	phenyl	p-nitrophenyl	240.5-242.5
67	p-ethyl	o-methylphenyl	p-fluorophenyl	143-144.2
68	p-ethyl	o-methylphenyl	p-nitrophenyl	157.2-158.6
69	o-methoxy	o-methylphenyl	p-fluorophenyl	133-135.5
70	o-methoxy	o-methylphenyl	p-nitrophenyl	178-180.5

- Cont'd -

Table 3 (Cont'd)

71	m-methoxy	phenyl	p-fluorophenyl	173.5-176.2
72	m-methoxy	phenyl	p-nitrophenyl	194.5-196.5
73	3,4-dimethoxy	phenyl	p-fluorophenyl	164.5-169
74	3,4-dimethoxy	phenyl	p-nitrophenyl	192-195
75	p-hydroxy	phenyl	p-nitrophenyl	166.5-167.5
76	p-fluoro	phenyl	p-fluorophenyl	209.5-211
77	p-fluoro	phenyl	p-nitrophenyl	225-226
78	p-fluoro	o-methylphenyl	p-fluorophenyl	157-159.5
79	p-fluoro	o-methylphenyl	p-nitrophenyl	193-195.5
80	o-fluoro	phenyl	p-fluorophenyl	191.3-192.2
81	o-fluoro	phenyl	p-nitrophenyl	224.8-226.7
82	o-chloro	phenyl	p-fluorophenyl	213.5-216
83	p-chloro	o-methylphenyl	p-fluorophenyl	150-151.5
84	p-chloro	o-methylphenyl	p-nitrophenyl	180-182
85	p-bromo	o-methylphenyl	p-fluorophenyl	157.4-158.7

- Cont'd -

Table 3 (Cont'd)

86	p-bromo	o-methylphenyl	p-nitrophenyl	180-180.5
87	o-bromo	phenyl	p-fluorophenyl	225-227
88	o-bromo	phenyl	p-nitrophenyl	210-212
89	p-cyano	o-methylphenyl	p-fluorophenyl	182.2-187.7
90	p-cyano	o-methylphenyl	p-nitrophenyl	180.5-183.7
91	H	p-methylbenzyl	p-nitrophenyl	147-148
92	H	p-methoxylbenzyl	p-nitrophenyl	110-112
93	H	p-fluorobenzyl	p-nitrophenyl	156.5-158.5
94	H	o-methoxybenzyl	p-nitrophenyl	146.5-148.5
95	H	o-trifluoromethylbenzyl	p-nitrophenyl	126-127.5
96	H	o-fluorobenzyl	p-nitrophenyl	116-117
97	H	m-chlorobenzyl	p-nitrophenyl	145-147
98	H	p-chlorobenzyl	p-nitrophenyl	157.5-159.5
99	H	m-trifluoromethylbenzyl	p-nitrophenyl	124-126
100	H	p-trifluoromethylbenzyl	p-nitrophenyl	107.5-109

- Cont'd -

Table 3 (Cont'd)

101	H	m-methoxybenzyl	p-nitrophenyl	124-126
102	H	3,4-methylenedioxybenzyl	p-nitrophenyl	148-151
103	H	2,4-dichlorobenzyl	p-nitrophenyl	96-98
104	H	3,4-dichlorobenzyl	p-nitrophenyl	145.5-148
105	H	1-naphthylmethyl	p-nitrophenyl	167.5-169
106	H	o-fluorobenzyl	p-fluorophenyl	96-97.5
107	H	m-methoxybenzyl	p-fluorophenyl	108-110.5
108	H	m-trifluoromethylbenzyl	p-fluorophenyl	100-102
109	H	p-trifluoromethylbenzyl	p-fluorophenyl	136-138
110	H	3,4-dichlorobenzyl	p-fluorophenyl	111-113
111	o-methyl	benzyl	p-nitrophenyl	111-114
112	p-methoxy	benzyl	p-nitrophenyl	127-128
113	p-fluoro	benzyl	p-nitrophenyl	118-120
114	m-chloro	benzyl	p-nitrophenyl	82-87
115	p-fluoro	o-chlorobenzyl	p-nitrophenyl	98.5-101.5

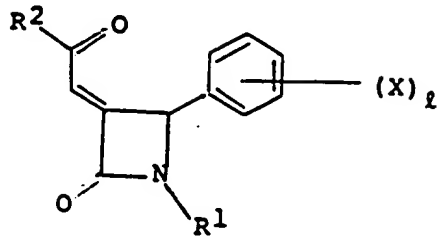
- Cont'd -

Table 3 (Cont'd)

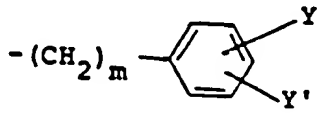
116	p-isopropyl	o-chlorobenzyl	p-nitrophenyl	155-156	
117	o-fluoro	o-chlorobenzyl	p-nitrophenyl	153.5-157	
118	p-trifluoro-methyl	o-chlorobenzyl	p-nitrophenyl	115.5-121.5	

Claims

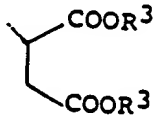
1. 2-Azetidinone derivatives represented by the following formula



wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, ℓ is 1 or 2, R^1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula



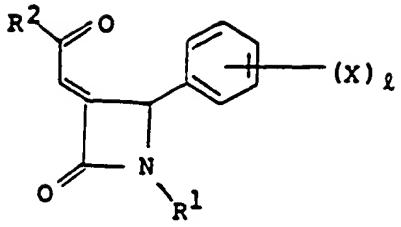
(wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula



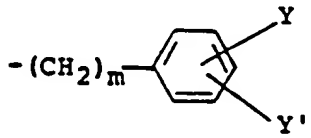
(wherein R^3 is a lower alkyl group), and R^2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxycarbonylmethyl group, or a group of the formula

(wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

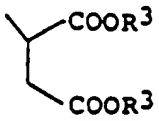
2. Blood platelet aggregation inhibiting agents containing 2-azetidinone derivatives represented by the general formula



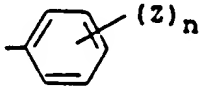
wherein X is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyl group or a cyano group, ℓ is 1 or 2, R^1 is a lower alkyl group, a cycloalkyl group, a 1-naphthylmethyl group, a 1-phenethyl group, 1-carboxy-2-phenethyl group, a group of the formula



(wherein Y and Y' are the same or different and each is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a dimethylamino group, a carboxyl group, a dichloroacetyl group or a trifluoromethyl group, or Y and Y' together form a methylenedioxy group, and m is 0 or 1) or a group of the formula



(wherein R^3 is a lower alkyl group), and R^2 is a lower alkyl group, a lower alkoxy group, an amino group, an adamantyl group, a lower alkoxycarbonylmethyl group, or a group of the formula

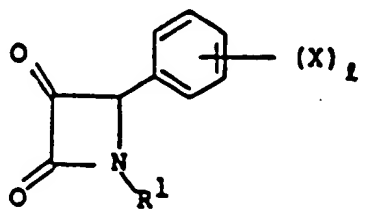


(wherein Z is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a phenyl group or a nitro group, and n is 1 or 2).

3. A 2-azetidinone derivative according to Claim 1, wherein the oxyalkylidene substituent has the E-configuation.

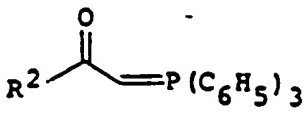
4. A 2-azetidinone derivative according to Claim 1 or Claim 3, wherein the configuration due to the asymmetric carbon atom at the 4-position is of the dl-form.

5. A process for producing a 2-azetidinone derivative of the formula given and defined in Claim 1, which comprises reacting a compound of the formula



II

wherein R^1, X and t are as defined in Claim 1, with a Wittig reagent of the formula



III

wherein R^2 is as defined in Claim 1.

6. A 2-azetidinone derivative of the formula given and defined in Claim 1 for use as a pharmaceutical.

7. A 2-azetidinone derivative of the formula given and defined in Claim 1 for use as a blood platelet aggregation inhibiting agent.

8. A pharmaceutical composition comprising a 2-azetidinone derivative of the formula given and defined in Claim 1 and a pharmaceutically acceptable diluent or carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 87308942.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
A	TETRAHEDRON, vol. 41, no. 2, 1985 MORI et al.: "New synthesis of β-lactames" pages 375-385 • Pages 381, 385 (compounds 20a, 20b, 20c, 20c') • --	1,3-5	C 07 D 205/08 A 61 K 31/395
A	LIEBIGS ANNALEN DER CHEMIE, 1983, Heft 5 H.-H. OTTO et al. "Darstellung und Stereochemie von 3-(α-Hydroxybenzyl)-1,4-diphenyl-2-azetidinonen" pages 1152-1168 • Pages 1153, 1158 (compounds 3,5); pages 1165-1168 (compounds 4,4f,8) • --	1,3-5	
A	ARCHIV DER PHARMAZIE, vol. 319, no. 3, March 1986 BERGMANN et al.: "Zur N- und O-Silylierung von β-Lactamen" pages 203-216 • Pages 208,214,215 (compounds 14,15) • --	1,3-5	TECHNICAL FIELDS SEARCHED (Int Cl 4) C 07 D 205/00 A 61 K 31/00
A	EP - A1 - 0 149 419 (NIPPON ZOKI PHARM.) • Page 1, last two lines; page 2; claims 15-19 • --	2,6-8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	07-01-1988	JANISCH

CATEGORY OF CITED DOCUMENTS

X particularly relevant if taken alone
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EUROPEAN SEARCH REPORT

Application number

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
D,A	TETRAHEDRON LETTERS, vol. 25, no. 42, 1984 MANHAS et al.: "A convenient synthesis of azetidine-2,3-diones" pages 4733-6 * Page 4735 * ----	5	

TECHNICAL FIELDS SEARCHED (Int Cl 4)

The present search report has been drawn up for all claims

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